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(6) Role of Endotoxin in the Pathogenesis of Louse-borne Relapsing Fever and in the Mechanism of the Jarisch-Herxheimer Reaction Following Treatment of Louse-borne Relapsing Fever.

by

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I. Introduction

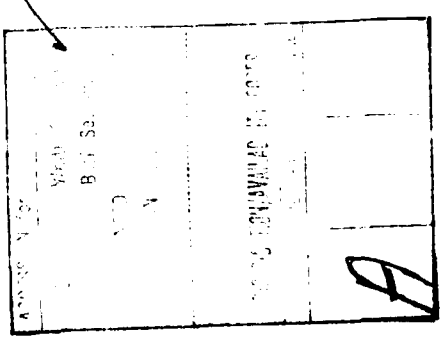
Louse-borne relapsing fever is an acute febrile illness caused by the spirochete Borrelia recurrentis and transmitted to man by infected body lice. It is endemic in Ethiopia and, if untreated, may have a mortality rate as high as 40% (1). While treatment with penicillin or tetracyclines greatly reduces the mortality rate to approximately 5% (2), antibiotic treatment typically induces severe rigors followed by a rise in temperature and a fall in blood pressure (3). This reaction, called a Jarisch-Herxheimer-like reaction, begins about two hours after initiation of treatment in most patients and is associated with the disappearance of spirochetes from the peripheral blood.

Previous studies of the pathophysiology of relapsing fever demonstrated cardiorespiratory disturbances (4), liver dysfunction (2), and abnormalities of blood coagulation consistent with disseminated intravascular coagulation (DIC), which worsen during the Jarisch-Herxheimer-like reaction (5,6). Because these findings suggested that relapsing fever might be associated with endotoxemia, evidence of circulating endotoxin has been sought. In a previous study, plasma obtained from 5 patients during the Jarisch-Herxheimer-like reaction was shown to be pyrogenic in normal, but not in endotoxin-refractory rabbits (7).

The purpose of the present study was to determine whether endotoxin, as detected by the highly sensitive limulus test (8-10), is present in the plasma of patients with relapsing fever before therapy and during the Jarisch-Herxheimer-like reaction. Further similarities between relapsing fever and Gram-negative bacteremic diseases were sought by examining plasma protein mediators of inflammation, including Hageman factor, prekallikrein, and the complement system, which are known to be activated during Gram-negative bacterial infections (11-17).

The aims of therapy should be to clear the blood of circulating spirochetes without relapse and to cure the acute illness without precipitating an unduly severe Jarisch-Herxheimer reaction. Tetracycline is the most frequently recommended treatment but often provokes a severe reaction. Only two other randomized clinical trials of antibiotics have been reported in louse-borne relapsing fever. In these studies, Rijkels [51] and Knaack et al [1] showed that pencillin G produced less severe reactions than tetracycline but cleared spirochetes more slowly with more prolonged fever. Single dose therapy with intravenous tetracycline [1,2] and oral doxycycline [18] has been shown effective, but other studies have used antibiotics for more than one day. If other antibiotics were also effective in single dose regimens, the mangement of patients could be made simpler and cheaper.

The present study seeks to compare erythromycin and tetracycline in single oral doses, as well to re-examine the differences between parenteral penicillin G and tetracycline. Because the Jarisch-Herxheimer reaction following antibiotics can be severe and even fatal [53] the antipyretic drug acetaminophen and anti-inflammatory drug hydrocortisone were examined for efficacy in preventing or ameliorating the Jarisch-Herxheimer reaction.



II. METHODS & MATERIALS

Fifteen febrile patients whose blood smears were positive for spirochetes characteristic of B. recurrentis were admitted to the research ward of the U.S. Naval Medical Research Unit No. 5 in Addis Ababa, Ethiopia. Signed informed consent was obtained from all patients. No patient had received earlier antibiotic treatment. After admission, each patient was given a single oral dose (100 mg.) of doxycycline, which was shown previously to be as effective as tetracycline (18).

Venous blood was collected in plastic, pyrogen-free syringes at the time of admission, two hours after treatment, and seven days after treatment. Platelets were determined by the direct counting method of Rees and Ecker (19). Fibrinogen levels were measured by the method of Ratnoff and Menzie (20). Fibrinogen-related antigens were measured by a latex slide agglutination test, the Thrombo-Wellco test (Wellcome Reagents, Ltd., England) (21). Spirochete concentrations were determined by counting the number of organisms per high power field in thin blood smears stained with Wright's stain.

Plasma for the limulus test was obtained from blood mixed with 75 units of heparin per ml and centrifuged at 500 x g for 5 min. The plasma was transferred to pyrogen-free bottles containing penicillin G (final concentration 100 units/ml) and streptomycin (final concentration 100 µg/ml) and frozen at -70°C until tested. Endotoxin was measured by the limulus test, as previously described (8-10). Plasma was initially extracted with chloroform for four hours. One lot of pooled lysate was used for all tests and detected 0.1 ng. of endotoxin per ml plasma. E. coli endotoxin (Lipopolysaccharide, E. coli B, 055:B5, Difco Laboratories, Detroit Mich.) was used as a standard. Positive results of flocculation (1+), increased turbidity and viscosity (2+), and complete gelation (3+) are semi-quantitatively related to the concentration of bacterial lipopolysaccharide in solution.

Studies of kinin generation and coagulation were performed using plasma obtained from blood drawn into 3.8% sodium citrate (1 part sodium citrate: 9 parts blood). Serum was obtained from blood samples allowed to clot at room temperature for 30 minutes. Within 5 minutes after initial processing, serum and citrated plasma were placed at -70°C and stored for not longer than three months before measurement of complement components, Hageman factor and prekallikrein.

Determinations of Hageman factor and plasma prekallikrein were performed with procoagulant assays, using congenitally deficient plasmas (22-24). One unit of activity was arbitrarily defined as that amount present in 1 ml of a standard pool of normal, citrated plasma. Total hemolytic complement activity (CH_{50}) was measured by a modification of the assay described by Mayer (25). Properdin activity was measured by the zymosan assay, as described by Pillemer, et al (26).

The significance of differences between the means of variables was determined by analysis of variance, by means of a stepwise regression program from the University of California performed on a PDP 1145 (Fortran V09.02) computer. Comparisons of means were made with the F-statistic (27).

Therapeutic trials. Twenty-one consecutive patients were randomly allocated to receive single doses of either tetracycline hydrochloride

(Lederle Laboratories, Pearl, N.Y.) 500mg orally or erythromycin stearate (Abbott Laboratories, North Chicago, Ill.) 500mg orally. Subsequently, thirty patients were randomly assigned to receive single doses of either tetracycline hydrochloride (Lederle Laboratories) 250mg intravenously or procaine penicillin G (Pfizer Laboratories Division, New York, N.Y.) 600,000 units intramuscularly. Nine patients were given potassium penicillin G (Pfizer Laboratories Divison, New York, N.Y.) 300,000 units intravenously. Another group of 15 patients, who received erythromycin orally, were randomly assigned to receive acetaminophen (McNeil Laboratories, Fort Washington, PA.) 650mg orally 2 hours before and 2 hours after erythromycin or hydrocortisone sodium succinate (The Upjohn Company, Kalamazoo, Mich.) 500mg intravenously 2 hours before and 2 hours after erythromycin or no drug in addition to erythromycin. All patients received approximately 1000 ml of normal saline by intravenous infusion every 4 hours during the first 12 hours in the hospital.

Hospital Courses. At hourly intervals beginning with the initiation of antibiotic therapy rectal temperatures and blood pressures were taken. After the temperature had reached $\leq 38^{\circ}C$, vital signs were taken routinely every 4 hours. Peripheral blood smears were obtained with finger lances and stained with Wright's stain at hourly intervals until they were negative for spirochetes and again at the time of discharge. Time intervals from the initiation of antibiotic therapy to the onset of rigor, maximal temperature, disappearance of spirochetes from blood, and defervescence ($T \leq 38^{\circ}C$) were calculated. Means of these time intervals and changes in vital signs were computed for each therapeutic regimen and compared by Student's t tests for independent samples [54].

III. Results

Patients. The 15 patients were Ethopians, whose ages ranged from 11 to 46 years, with a mean of 21 years. There were 12 males and 3 females. All had been previously healthy and did not have histories of concomitant diseases. The duration of fever before admission ranged from 4 to 15 days, with a mean of 6.4 days. The initial diagnosis was based on a Wright's stain of peripheral blood that revealed spirochetes, which ranged in concentration from 4 to 15 spirochetes per high-power field. Blood cultures showed no growth of bacteria in all cases.

Hospital courses. Approximately 2 hours after doxycycline treatment, all patients experienced an increase in symptoms, with chills, rising temperature, and increasing prostration. At this time, spirochetes either could not be demonstrated in a blood smear or were greatly diminished in concentration. This Jarisch-Herxheimer-like reaction to treatment lasted approximately 2 hours, after which time the patients felt improved. There was no clinical evidence of abnormal hemostasis and no deaths occurred. The mean white blood cell count of these patients was $8.7 \times 10^9/l$ at the time of admission. Two hours after treatment the mean white blood cell count had decreased significantly to $5.7 \times 10^9/l$ ($P<0.05$); during convalescence it rose to $8.5 \times 10^9/l$.

Vital signs. At the time of admission the mean temperature of these patients was 39.3°C and the mean pulse rate 118 per minute. Two hours after treatment, the mean temperature rose to 40.9°C and the pulse rate to 138 per minute. During convalescence, seven days later, the mean temperature

was 37.1°C and the pulse rate 79 per minute. Blood pressure (mean systolic/mean diastolic in mm Hg) at the time of admission was 107/66, and fell to 83/55 two hours after treatment. The mean of the blood pressures rose to 114/70 at the time of convalescence.

Coagulation studies. The mean platelet count, which was low at the time of admission ($46_9 \times 10^9/l$), decreased additionally two hours after treatment to $26 \times 10^9/l$ ($P<0.05$) (Table 1). During convalescence, the mean platelet count rose significantly ($P<0.01$) to a normal value of $304 \times 10^9/l$. The mean fibrinogen concentration remained within the normal range during all times of examination. The mean partial thromboplastin time at the time of admission was 13 seconds longer than the mean of the controls. This prolongation increased further to 25 seconds at 2 hours after treatment ($P<0.01$) but then decreased to only a 3 second difference during convalescence ($P<0.01$). Means of both Hageman factor and prekallikrein activity were decreased at the time of admission and 2 hours after treatment (Table 1). During convalescence, the means increased significantly to the normal range ($P<0.05$). The frequency of elevated concentrations of fibrinogen-related antigens at the time of admission (3/15) increased significantly to 12/15 two hours after treatment ($P<0.01$). During convalescence, none of the patients had elevated concentrations of fibrinogen-related antigens.

Complement system. At the time of admission, the mean serum hemolytic complement activity was diminished to 69 units/ml (normal is 100 ± 20 units/ml) and remained diminished two hours after treatment (Table 2). During convalescence the mean concentration rose to the normal range and was significantly greater than at the time of admission and two hours after treatment ($P<0.01$). At the time of admission and two hours after treatment, properdin titers were decreased in 14 and 12 patients, respectively. Seven days after treatment, all retested patients had normal properdin levels. The decreased frequency of reduced properdin titers during convalescence was significant ($P<0.01$).

Limulus tests for endotoxin in plasma. The results were semi-quantified according to the extent of the gelation reaction: flocculation = 1+, increased turbidity and viscosity = 2+, and complete gelation = 3+. The plasma of 11 patients at the time of admission and of 13 patients tested two hours after treatment produced positive tests. During convalescence, only 4 of 13 retested patients were positive (Table 3). The differences in frequency of positivity of the limulus tests between the time of convalescence and both admission and two hours after treatment were statistically significant ($P<0.01$).

A positive correlation was present between the concentration of spirochetes in plasma at the time of admission and the semi-quantitative results of the limulus test two hours after treatment. Spirochete concentrations were graded as 1 (≤ 5 spirochetes per high power field [HPF]), 2 (6-10 spirochetes per HPF), and 3 (11-15 spirochetes per HPF). Of 9 patients with spirochete concentrations of grades 1 and 2, 2 patients had negative limulus tests and 7 had 1+ results. In contrast, none of six patients with an initial spirochete concentration of grade 3 had a negative limulus test; 3 patients had 1+ results and 3 had 2+ results.

Therapeutic trials. All twenty-one patients receiving oral tetracycline or erythromycin responded favorably with disappearance of spirochetes and defervescence. Rigors were experienced by 10 of 11 patients receiving

tetracycline and 8 of 10 patients receiving erythromycin. There were no significant differences in the rapidity of onset of the Jarisch-Herxheimer reaction or in the severity of changes in vital signs between the 2 groups (table 4). These results demonstrated that these two treatments were equally effective.

All thirty patients assigned to receive either tetracycline intravenously or procaine penicillin G intramuscularly responded favorably and were cured. The onset of the rigor, however, was delayed in the group receiving penicillin G (table 4). Likewise, there were significantly longer intervals ($P<0.05$) from the initiation of therapy to the maximal temperature, disappearance of spirochetes from blood, and the time of defervescence in the group treated with penicillin G. The mean rises in temperature and falls in blood pressures were less in the group treated with penicillin than with tetracycline, but only the difference in diastolic blood pressures was statistically significant ($P<0.05$). All 15 patients treated with tetracycline experienced rigors, whereas only 10 of the 15 patients treated with penicillin G had rigors.

To determine whether the slower action of penicillin G was attributable to slow absorption of the procaine salt from the intramuscular site nine patients were given penicillin G 300,000 units intravenously. These nine patients experienced rigors at a mean time of 1.6 hours after therapy. One patient failed to clear blood spirochetes after 24 hours and was given erythromycin. The mean times of 19.3 hours to defervescence and 13.0 hours for 8 patients to clear blood spirochetes were significantly longer ($P<0.005$) than these times in patients receiving intravenous tetracycline.

Pre-treatment with acetaminophen and hydrocortisone did not prevent the rigors of the Jarisch-Herxheimer reaction, as all patients except one in the control group had rigors after receiving erythromycin. Nor did these drugs alter the time of onset of rigors, time of reaching maximal temperature, and time for disappearance of spirochetes from blood after erythromycin therapy (table 5). Defervescence did, however, occur earlier in the hydrocortisone-treated group, in 7.6 hours, than in the other two groups ($P<0.05$). The magnitude of temperature rise after erythromycin was less in the hydrocortisone group (2.1°C), but the difference between the control group was not statistically significant. The falls in systolic blood pressures were significantly lower in the both the acetaminophen and hydrocortisone groups than in the control group ($P<0.05$).

Hospital courses. All patients, while receiving intravenous normal saline at a rate of approximately 1000cc every 4 hours, showed decreases in blood pressure during the first 8 hours after antibiotic therapy. Only one patient developed shock and he responded to additional saline infusion. No patient developed congestive heart failure.

Eighteen patients, or 35% of the patients in the randomized antibiotic studies, had a return of temperature >38°C after the initial defervescence. Blood smears for spirochetes were negative in all cases, and these fevers were transient. At the time of discharge, after approximately one week of observation, routine blood smears were negative for spirochetes in all patients. Thus, there was no evidence for relapses.

IV. Discussion

Our clinical and laboratory observations of 15 patients with louse-borne relapsing fever confirm and extend the studies of our predecessors in Ethiopia (1-7, 28-30). All of our patients were febrile and had spirochetes in their peripheral blood smears at the time of admission. Approximately two hours after treatment with doxycycline, all patients experienced rigors followed by a rise in temperature and a fall in blood pressure, characteristic of the Jarisch-Herxheimer-like reaction of relapsing fever (3). At this time, the spirochetemia had disappeared or was diminishing. Our laboratory results confirmed the previous observations of abnormalities of blood coagulation, including thrombocytopenia and prolonged partial thromboplastin times (5). During the Jarisch-Herxheimer-like reaction, the white blood cell counts and platelet concentrations decreased and the serum levels of fibrinogen-related antigens increased in most of our patients, as reported previously (6,30).

The previously undescribed abnormalities of blood coagulation are decreased plasma levels of Hageman factor and prekallikrein activity. Endotoxin, demonstrated in the blood of these patients with the limulus test, directly activates Hageman factor (31). Activated Hageman factor not only triggers the intrinsic coagulation pathway but converts prekallikrein to kallikrein, which releases kinins from kininogen (32). Kinins are small peptides, which dilate small blood vessels and reduce blood pressure, and have been implicated as among the mediators of endotoxin shock (11). Although plasma levels of Hageman factor and prekallikrein were greatly diminished at the time of admission, they did not decrease significantly further after treatment. In contrast, other coagulation studies showed significant worsening during the Jarisch-Herxheimer-like reaction. This suggests that laboratory abnormalities compatible with DIC, present at the time of admission, may be mediated at least in part by activation of Hageman factor. However, exacerbations of the abnormalities of coagulation that followed the administration of an antibiotic may have been mediated by some additional mechanism. One possibility is acute blockade of the reticuloendothelial system by released spirochetal products, with consequent intravascular accumulation of products of fibrin and fibrinogen degradation or of intermediates of fibrin formation, some of which possess anticoagulant properties. This series of events appears to occur following the provocative dose of endotoxin in the animal model of the generalized Shwartzman reaction (12,33,34).

Activation of the complement system in relapsing fever was shown by decreased serum concentrations of hemolytic complement activity and properdin. Hemolytic complement activity is decreased by activation of either the classical or the alternate pathway. Properdin is a component of the alternative pathway of complement, that can be directly activated by endotoxin (35,36). Because we did not examine C1, C2, or C4 in the classical pathway, it cannot be inferred from our studies whether the alternative pathway alone had been activated, or whether both complement pathways were activated. Nevertheless, the anaphylatoxic activity of C3a and C5a may explain the more protracted vasodilation and altered hemodynamics observed during the Jarisch-Herxheimer-like reaction (14-16).

This study is the first application of the limulus test for the detection of endotoxin in this disease. The limulus test has been used

successfully to detect endotoxin or endotoxin-like material in blood in other disorders (9,37-40), although some investigators have not found it useful (41,42). Some substances, other than endotoxin, have been reported to produce a positive limulus test (43); another study, however, did not confirm some of these observations (44). At any rate, these substances either do not occur naturally or are proteins that probably would have been removed by the chloroform extraction of plasma, performed in preparation for the limulus tests (9,10,39).

Of fifteen patients with spirochetemia, 11 patients at the time of admission and 13 patients two hours after treatment had positive limulus tests. Seven days after therapy, only 4 patients had positive limulus tests. These results confirm the earlier attempts of Bryceson, et al (7) to demonstrate endotoxemia by re-infusion of patients' plasma into normal and endotoxin-refractory rabbits. Our method of obtaining plasma by low-speed centrifugation yielded plasma rich in spirochetes, white blood cells, and platelets. Therefore, positive limulus tests did not distinguish between endotoxin associated with spirochetes or present in the plasma and perhaps bound to white blood cells or platelets.

Patients with secondary syphilis were recently reported to have positive plasma limulus tests during the Jarisch-Herxheimer reaction associated with treatment, but had negative limulus tests both before and after the reaction (45). Although these findings were attributed to the release of "treponemal lipopolysaccharides" from dying spirochetes, there is little evidence to suggest that spirochetes possess endotoxin with biological activites identical to the lipopolysaccharides of Gram-negative bacteria. Treponemes have been shown to contain lipopolysaccharide (46), but extracted spirochetal lipopolysaccharides contained *no* pyrogenic activity for rabbits (47). Borreliae have been shown to contain cholesterol, lecithin and other uncharacterized lipids (48), but tests of biological activity were not carried out by the investigators. Mergenhagen et al extracted lipopolysaccharides from Borrelia vincentii, B. buccalis, and small oral treponemes and found them to be pyrogenic and to prepare rabbits' skin for the local Shwartzman reaction (49). On a weight basis, however, the treponemal extracts were much less potent than bacterial products.

One cannot exclude the possibility, however, that some manifestations of louse-borne relapsing fever, particularly the Jarisch-Herxheimer-like reaction, result from the leakage of endotoxin from the Gram-negative bacteria of the gastrointestinal tract into the circulation (37,50). This latter proposal is strengthened by our observations that concentrated preparations of both borrelial and treponemal organisms produced negative Limulus test results (J. Levin and T. Butler, unpublished observations). Since our studies demonstrated a semi-quantitative relationship between the concentration of spirochetes in blood and the concentration of circulating endotoxin or endotoxin-like material, our data may reflect a relationship between the level of spirochetemia and the total body burden of B. recurrentis. Excessive numbers of spirochetes or their products may block the normal function of the reticuloendothelial system. Subsequently, bacteria or bacterial products which enter the circulation from the gastrointestinal tract may not be effectively cleared (37,50), a process which may account for the activation of coagulation, complement, and prekallikrein that was observed.

In the treatment of B. recurrentis infection, tetracycline is usually considered the drug of choice (1,2,55). Although single dose therapy with intravenous tetracycline (1,2,51) and oral doxycycline (18) has been used successfully, other workers recommend or have used tetracycline for several days (2,51,52,55). The present study demonstrated that single oral doses of 500mg of both tetracycline and erythromycin were highly effective in clearing blood spirochetes and preventing relapses. Both drugs provoked typical Jarisch-Herxheimer reactions in most cases, but none of the patients died while being supported by intravenous normal saline. The usefulness of erythromycin as an alternative to tetracycline will be for pregnant patients and children, in whom tetracycline should be avoided to prevent staining of developing teeth.

Our results of therapy with penicillin G confirm the observations of Rijkels (51) and Knaack et al (1) that penicillin clears the blood of spirochetes more slowly and provokes a Jarisch-Herxheimer reaction less frequently than tetracycline. The slow action of penicillin could not be attributed to slow absorption from intramuscular injections because intravenous penicillin also acted slowly. Furthermore, the patients given intravenous penicillin experienced rigors early that were temporally dissociated from a delayed clearing of blood spirochetes. The failure of penicillin to clear blood spirochetes after 24 hours in one of our patients combined with other reports of failure and relapses with penicillin (12,51) argue against its use in this disease. Others have suggested that penicillin be given on the first day followed by tetracycline on subsequent days in order to avoid severe Jarisch-Herxheimer reactions (1,2,52). We do not believe that this regimen is necessary because the Jarisch-Herxheimer reactions, although uncomfortable and distressing, lasted only about 30 minutes and were never fatal in our patients.

In an attempt to minimize the severity of the Jarisch-Herxheimer reaction, acetaminophen and hydrocortisone were used. Hydrocortisone had been used by others in doses of 100mg intravenously [3] and 20mg/kg/hr intravenously [2] without effect other than lowering the body temperature. In this study, five patients received 500mg of hydrocortisone 2 hours before and 2 hours after erythromycin. Although the temperature rose less and defervescence occurred earlier with hydrocortisone, the Jarisch-Herxheimer reaction was not prevented. Both acetaminophen and hydrocortisone significantly reduced the fall in systolic blood pressure following erythromycin therapy, but we believe the magnitudes of the difference do not justify the routine use of these drugs in the treatment of relapsing fever.

From the results of our studies, optimal antibiotic therapy for relapsing fever is a single oral dose of 500mg of either tetracycline or erythromycin. Patients unable to take oral medication can be treated with tetracycline 250mg intravenously. One must anticipate a Jarisch-Herxheimer reaction and prevent hypotension with intravenous saline infusion. With this approach to the therapy of louse-borne relapsing fever, the mortality rate should be nearly zero without relapse, and patients can be discharged after a short hospitalization.

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VI. Significant Accomplishments

The roles of certain plasma proteins and endotoxin in the pathogenesis of Borrelia recurrentis infection were studied in 15 patients. Mean titers of Hageman factor, prekallikrein, and hemolytic complement were decreased at the time of admission and 2 hours after treatment during the Jarisch-Herxheimer-like reaction (JHR). Serum properdin titers were decreased in 14 patients at the time of admission and in 12 patients, 2 hours after treatment. Limulus tests for endotoxin were positive in 11 patients at the time of admission and in 13 patients 2 hours after treatment. During the JHR, the frequency of elevated fibrinogen-related antigens increased from 3 patients to 12 patients. These findings indicate that plasma protein systems are activated in B. recurrentis infection and that endotoxin may have a role in both the acute illness and in the development of the JHR after treatment.

To evaluate single dose antibiotic regimens in Borrelia recurrentis infection, fifty-one patients with louse-borne relapsing fever were randomly assigned either to one of the oral antibiotic regimens tetracycline 500 mg or erythromycin 500 mg or to one of the parenteral regimens tetracycline 250 mg intravenously or procaine penicillin G 600,000 units intramuscularly. Another fifteen patients were randomly treated with acetaminophen 1.3 g orally, hydrocortisone 1 g intravenously, or nothing in combination with erythromycin to evaluate the effect of these drugs on the severity of the Jarisch-Herxheimer reaction. Vital signs were measured hourly until stable and blood smears for spirochetes were obtained hourly until negative. All patients survived and there were no relapses. Oral tetracycline and erythromycin caused defervescence and cleared blood organisms equally rapidly and produced similar changes in temperatures and blood pressures. Penicillin G intramuscularly produced defervescence more slowly than intravenous tetracycline (14.4 hours vs. 10.5 hours) and cleared blood organisms more slowly (9.0 hours vs. 3.1 hours). Therapy with acetaminophen and hydrocortisone modified the changes of vital signs during the Jarisch-Herxheimer reaction but did not prevent rigors. It is concluded that a single oral dose of 500 mg of tetracycline or erythromycin is optimal therapy for B. recurrentis infection.

VII. Bibliography

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Table 1. Coagulation studies in 15 Patients with Borrelia recurrentis infection.*

	Admission	Two hours Post-treatment	Convalescence
Platelets x 10^9/l (normal 150-350 x 10^9/l)	46 ± 33	26 ± 14	304 ± 161
Fibrinogen, g/l (normal 2.0-4.0 g/l)	3.7 ± 0.7	3.3 ± 0.9	2.8 ± 0.9
Partial thromboplastin time, seconds beyond mean of controls**	13 ± 16	25 ± 13	3 ± 3
Hageman factor, units/ml (normal 1.09 ± 0.37 units/ml)	0.33 ± 0.17	0.41 ± 0.28	0.95 ± 0.10
Plasma prekallikrein, units/ml (normal 0.95 ± 0.18 units/ml)	0.39 ± 0.18	0.34 ± 0.14	0.97 ± 0.11
Fibrinogen-related antigens***	3/15	12/15	0/15

* Values expressed as mean ± 1 standard deviation.

** Mean of controls was 40 seconds.

*** Measured by a slide test and expressed as the ratio of patients with elevated concentrations of fibrinogen-related antigens ($\geq$ 40 µg/ml) to the total number of patients tested.

Table 2. Activation of the Complement System in 15 patients with Borrelia recurrentis infection

	Complement* (mean CH_{50} Units ± 1 Standard Deviation)	Properdin** (Ratio of patients with <4 Units/ml to the number tested)
Admission	69 ± 32	14/15
Two hours after treatment	66 ± 33	12/14
Convalescence	120 ± 22	0/6

* Normal CH_{50} values for this laboratory are 100 ± 20 units/ml.

** Normal properdin levels for this laboratory are $\geq$ 4 units/ml.

Table 3. Semi-quantitative limulus tests in 15 patients with *Borrelia recurrentis* infection*

	3+	2+	1+	0
Admission	1	0	10	4
Two hours after treatment	0	3	10	2
Convalescence	0	0	4	9

* The results of semi-quantitative limulus tests were read as: 0 = No reaction; 1+ = flocculation; 2+ = increased turbidity and viscosity; and 3+ = complete gelation.

Table 4. Randomized clinical trials of single dose antibiotic regimens comparing tetracycline hydrochloride with erythromycin stearate as oral doses of 500 mg and comparing tetracycline hydrochloride 250 mg i.v. with procaine penicillin G 600,000 units i.m.

	Mean Values ± 1 Standard Deviation			
	Oral Regimens		Parenteral Regimens	
	Tetracycline	Erythromycin	Tetracycline	Penicillin G
Intervals, in hours, between initiation of therapy and:				
Onset of rigor*	2.3 ± 0.7	2.3 ± 0.8	1.1 ± 0.4	1.8 ± 0.5†
Maximal temperature	3.4 ± 0.9	3.8 ± 1.0	2.8 ± 1.1	3.8 ± 1.2†
Disappearance of spirochetes from blood	3.6 ± 1.4	3.6 ± 1.6	3.1 ± 1.2	9.0 ± 7.3†
Defervescence (rectal temperature ≤ 38 degrees)	12.8 ± 3.5	13.8 ± 4.1	10.5 ± 2.9	14.4 ± 4.6
Changes in vital signs after initiation of therapy:				
Rise in temperature to maximum in degrees	2.3 ± 0.3	2.2 ± 0.7	2.7 ± 0.8	2.4 ± 0.7
Decrease in blood pressure to minimum in mm Hg				
Systolic	28 ± 10	31 ± 11	34 ± 16	29 ± 12
Diastolic	24 ± 11	26 ± 10	31 ± 15	21 ± 11‡

*Rigor was experienced by the following proportions of patients: 10/11 tetracycline p.o., 8/10 erythromycin p.o., 15/15 tetracycline i.v., and 10/15 penicillin G i.m.

†Time intervals significantly longer for penicillin G than for tetracycline i.v. by student's t test ($P<0.05$).

‡Decrease in blood pressure significantly less for penicillin G than for tetracycline i.v. by student's t test ($P<0.05$).

Table 5. Randomized clinical trial of acetaminophen and hydrocortisone combined with erythromycin stearate in Borrelia recurrentis infection.

	Mean Values ± 1 Standard Deviation Unit		
	Control (5 patients)	Acetaminophen (5 patients)	Hydrocortisone (5 patients)
Interval, in hours, between initiation of antibiotic therapy and:			
Onset of rigor	2.9 ± 1.7	2.0 ± 0.5	2.5 ± 1.0
Maximal temperature	3.3 ± 0.8	2.6 ± 0.6	3.8 ± 1.2
Disappearance of spirochetes from blood	4.4 ± 2.3	3.0 ± 0.7	3.4 ± 1.5
Defervescence (rectal temperature ≤ 38 degrees)	11.4 ± 2.6	12.8 ± 1.3	7.6 ± 1.3*
Changes in vital signs after initiation of antibiotic therapy:			
Rise in temerpature to maximum in degrees	2.4 ± 0.5	2.9 ± 0.2	2.1 ± 0.6
Decrease in blood pressure to minimum, in mm Hg			
Systolic	29 ± 13	15 ± 6	17 ± 4†
Diastolic	17 ± 5	13 ± 8	14 ± 6

*Defervescence occurred earlier in hydrocortisone group than in other two ($P<0.05$ by t tests)

†Decreases in systolic blood pressures less in both acetaminophen and hydrocortisone groups than in control ($P<0.05$ by t tests)

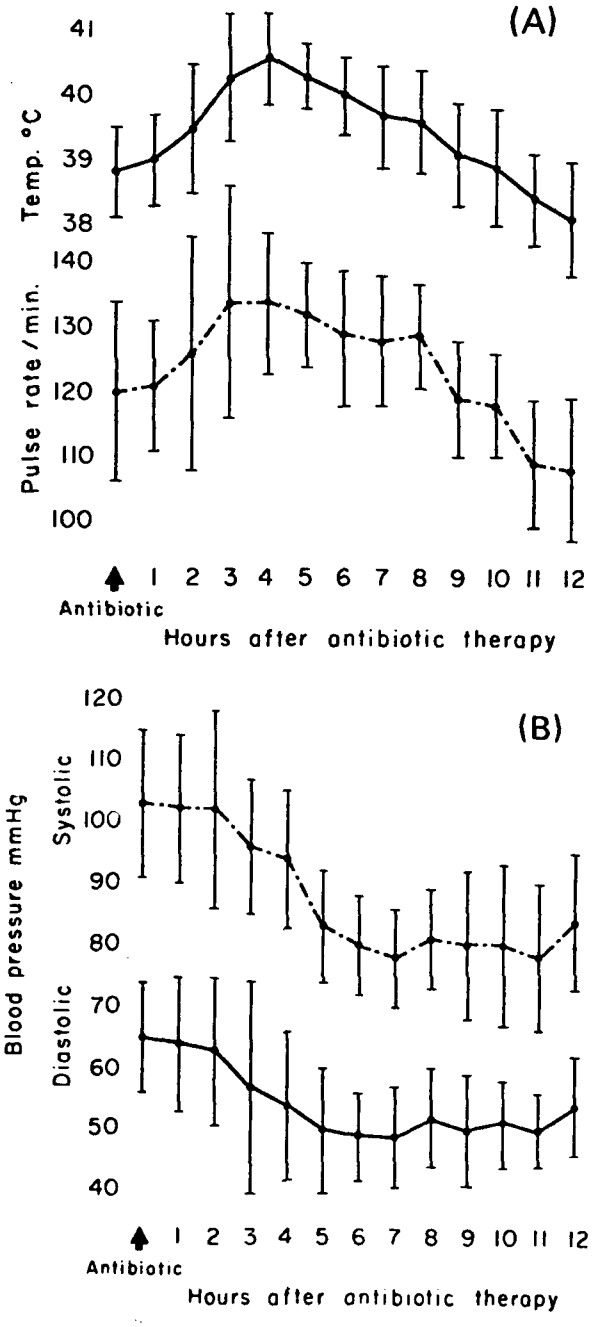

Figure 1. Means and standard deviations of temperatures, pulses, and blood pressures in 21 patients with louse-borne relapsing fever during 12 hours after treatment with oral tetracycline or erythromycin 500mg.

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